UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,639	09/18/2003	Timothy Vickers	CORE0027US	4524

32650 7590 06/12/2007
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
06/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,639	VICKERS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90,93 and 94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90, 93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 6-30-06.

Claims 90, 93 and 94 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 90, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 10-2-06.

The claims are drawn to compositions and methods for eliciting cleavage of any target mRNA in a cell in vitro or in vivo comprising contacting the cell with an antisense oligoribonucleotide 12-30 nucleobases in length targeted to the RNA, which antisense oligoribonucleotide comprises no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3' terminus, and optionally further comprises phosphorothioate internucleoside linkages and 2'-fluoro modifications on or throughout the oligoribonucleotide.

Applicant's arguments filed 10-2-06 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the broad genus of compounds claimed because the limitations in the claims recite

particular lengths for the oligonucleotides, recite that no more than two mismatched nucleobases within the oligonucleotides, as well as reciting various modifications. Applicant also argues that an exhaustive list of every embodiment falling within the scope of the claims need not be provided to satisfy written description requirements.

Contrary to Applicant's assertions, he specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus comprising these compounds that specifically hybridize and successfully elicit cleavage in any target gene in a cell in vitro or in vivo. The specification teaches a method of eliciting cleavage of PTEN mRNA using the particularly described mismatched oligoribonucleotides shown in Table VI, VII and VIII in vitro, and methods of eliciting cleavage of PTEN mRNA in vitro comprising the administration of siRNAs specifically targeting PTEN U92436, and with dTdT additions at the 3' end of each siRNA strand (Tables I and II, pages 31-33 of the specification). The genus of nucleic acids claimed, however, is expansive and encompasses a myriad of structures (*e.g.* thousands and thousands of nucleic acid sequences) and the specification and claims do not adequately teach a representative number of species for the broad genus claimed. And, contrary to Applicant's assertions, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed, comprising antisense oligoribonucleotides between 12-30 nucleobases in length targeted to any RNA, which antisense oligoribonucleotides comprise no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3'terminus, and optionally further

comprise phosphorothioate internucleoside linkages and 2'-fluoro modifications on or throughout the oligoribonucleotides, and which provide for the function claimed, of eliciting cleavage of any target mRNA in cells in vitro or in vivo. Since the genus is so expansive, the species and guidance provided in the instant application are not representative of very broad genus of molecules claimed. For these reasons, the instant rejection is maintained.

Claims 90, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliciting cleavage of PTEN using the particularly described mismatched oligoribonucleotides shown in Table VI, VII and VIII in vitro, does not reasonably provide enablement for methods of eliciting cleavage of any target mRNA in a cell in vitro or in vivo comprising contacting the cell with an antisense oligoribonucleotide 12-30 nucleobases in length targeted to any target RNA, which antisense oligoribonucleotide comprises no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3' terminus for the reasons of record set forth in the Office action mailed 10-2-06.

Applicant's arguments filed 10-2-06 have been fully considered but they are not persuasive. Applicant argues that the full scope of the claims is enabled because the specification provides specific guidance to enable the full scope of the invention and that no undue experimentation is required to practice the full scope of the claimed invention.

Contrary to Applicant's assertions, it would require undue experimentation beyond that provided in the specification to enable the full scope of the claims. The claims are drawn to compositions and methods for eliciting cleavage of any target mRNA in a cell in vitro or in vivo comprising contacting the cell with an antisense oligoribonucleotide 12-30 nucleobases in length targeted to the RNA, which antisense oligoribonucleotide comprises no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3' terminus, and optionally further comprises phosphorothioate internucleoside linkages and 2'-fluoro modifications on or throughout the oligoribonucleotide.

The specification teaches a method of eliciting cleavage of PTEN mRNA using the particularly described mismatched oligoribonucleotides shown in Table VI, VII and VIII in vitro, and methods of eliciting cleavage of PTEN mRNA in vitro comprising the administration of siRNAs specifically targeting PTEN U92436, and with dTdT additions at the 3' end of each siRNA strand (Tables I and II, pages 31-33 of the specification). Applicants have not provided adequate guidance in the specification, however, toward a method of eliciting cleavage of any target mRNA in a cell in vitro or in vivo comprising contacting the cell with an antisense oligoribonucleotide 12-30 nucleobases in length targeted to the RNA, which antisense oligoribonucleotide comprises no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3'terminus, whereby a representative number of species of mismatched oligoribonucleotides have been described that provide for the elicitation of cleavage of any target mRNAs in vitro or in vivo.

Contrary to Applicant's assertions, one skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition using the particularly described mismatched oligoribonucleotides shown in Table VI, VII and VIII in vitro, or the siRNAs specifically targeting PTEN U92436, and with dTdT additions at the 3' end of each siRNA strand (Tables I and II, pages 31-33 of the specification) as being correlative or representative of the ability to elicit cleavage of any target mRNA in a cell in vitro or in vivo comprising contacting the cell with any antisense oligoribonucleotide 12-30 nucleobases in length targeted to any target RNA, which antisense oligoribonucleotide comprises no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3'terminus.

Contrary to Applicant's assertions, the art is quite unpredictable regarding the ability to elicit cleavage of any target messenger RNA in a cell in vivo using the broad genus of compounds claimed. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of antisense oligoribonucleotides 12-30 nucleobases in length targeted to the RNA, which antisense oligoribonucleotides comprise no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3'terminus, and which provide for the elicitation of cleavage of any target mRNA in vitro and in vivo. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds are effectively delivered in adequate quantities to the target cells, and cleavage of any target mRNA is

elicited. Since the specification fails to provide sufficient guidance for the methods claimed, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed. For these reasons, the instant rejection is maintained.

Claims 90, 93 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire and Zamore et al and Elbashir et al, in view of McKay insofar as the claims are drawn to compositions and methods of eliciting the cleavage of a target mRNA in vitro comprising administration of siRNA oligoribonucleotides that specifically hybridize to the target gene (of known sequence) in vitro, and which siRNA comprise 12-30 nucleobases in length, comprise no more than two mismatched nucleobases relative to the target RNA and 2'-O-modifications on the 3'terminus, and optionally further comprise phosphorothioate internucleoside linkages and 2'-fluoro modifications on or throughout the oligoribonucleotide molecule for the reasons of record set forth in the Office action mailed 10-2-06.

Applicant's arguments filed 10-2-06 have been fully considered but they are not persuasive. Applicant argues that the instant rejection is not obvious because the references relied upon in the obviousness rejection, Fire, Elbashir and Zamore, teach away from the instant invention because the claims are now limited to single stranded oligonucleoitdes and these teachings concern dsRNA. Applicant also argues that McKay does not teach the modifications at each residues, or at the positions recited in the instant claims, and therefore does not teach the limitations of the claimed invention.

Applicant is correct that Fire, Elbashir and Zamore are primarily concerned with dsRNA. But, contrary to Applicant's assertions, the fact that Fire compares the ability of dsRNA to inhibit expression of a target gene with ssRNA is not the same as teaching away from single stranded antisense mediated inhibition. It was routine at the time of the instant invention to use antisense to target and inhibit expression of a known target gene in vitro. It was routine to incorporate the modifications claimed (as evidenced by the teachings of McKay). The modifications claimed were well known to enhance target binding, cellular uptake and oligonucleotide stability in oligonucleotides, including single stranded antisense. The positions and extent of modifications incorporated into the oligonucleotides are merely a design choice. For these reasons, the instant rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

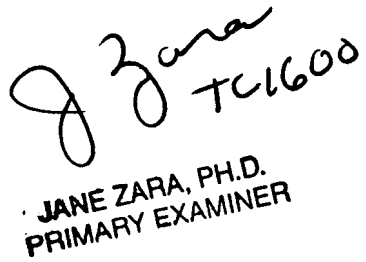
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
6-8-07



JANE ZARA, PH.D.
PRIMARY EXAMINER